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Short Communication

Early Clinical Outcomes of Anal Squamous Cell Carcinoma Treated with Concurrent Chemoradiotherapy with 5-Fluorouracil Plus Mitomycin C in Japanese Patients: Experience at a Single Institution

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Concurrent chemoradiotherapy with 5-fluorouracil plus mitomycin C has been established as a standard therapy for non-metastatic anal squamous cell carcinoma in the West. However, there have been few reports of chemoradiotherapy for anal squamous cell carcinoma in Japan. We retrospectively investigated seven consecutive anal squamous cell carcinoma patients who were treated with concurrent chemoradiotherapy consisting of 5-fluorouracil plus mitomycin C with a total irradiation of 59.4 Gy. The patients consisted of two males and five females. Clinical stages II/IIIA/IIIB accounted for four, one and two patients, respectively. Full-dose irradiation was completed in all patients. Median relative dose intensities of 5-fluorouracil and mitomycin C were both 99%. All patients achieved complete response. At a median follow-up of 37.5 months, one patient experienced local recurrence. The most common grade 3/4 acute toxicities were dermatitis in 100% and anal pain in 71%. There was no treatment-related death. Concurrent chemoradiotherapy appears to be tolerable and effective in Japanese patients with anal squamous cell carcinoma.

Key words: anal squamous cell carcinoma – chemoradiotherapy – 5-fluorouracil – mitomycin C

INTRODUCTION

Anal canal cancer is an uncommon disease, accounting for only 1.9% of gastrointestinal cancers in the USA, with an estimated 5290 new cases in 2009 (1). The incidence of anal canal cancer in the general population has increased over the last 30 years, from 10 to ~20 per million (2). In the past, anal canal cancer was routinely treated by abdominoperineal resection (APR), a radical procedure that involves the removal of the anorectum and the creation of a permanent colostomy. In an early series, the 5 year survival following APR for anal canal cancer was 40–70%, with a perioperative mortality of 3% (3–7). A subsequent small case series of patients with squamous histology treated with chemoradiotherapy (CRT) without APR showed a 5 year overall survival of 67% and a 5 year colostomy-free survival of 59% (8). This good clinical outcome with CRT for anal squamous cell carcinoma (ASCC) was confirmed in several randomized phase III trials, and CRT consisting of 5-fluorouracil (5-FU) plus mitomycin C (MMC) is now the standard of care for patients with ASCC in terms of better prognosis with anal preservation (9–16). All of these studies were conducted in Western populations, however, and the efficacy of CRT in Asian populations has not been reported.

Although the incidence of anal canal cancer in Japan has not been accurately determined, a population survey report in 2003 published by the Japanese Ministry of Health, Labour and Welfare stated that 261 patients had died of this disease, accounting for 0.67% of all large intestinal cancer deaths. Given that the incidence of anal canal cancer has doubled in the past 30 years in the West, the incidence in Japan is expected to increase as well. The only report of current therapeutic strategies for ASCC published in Japan reported that concurrent CRT was adopted in only 45% of patients, of whom only five were treated by a regimen of 5-FU plus MMC, without providing any further detailed information (17).

To our knowledge, few reports of concurrent CRT consisting of 5-FU plus MMC in patients with ASCC have been published in Asian countries, including Japan. Here, we retrospectively report seven patients with ASCC who were treated with concurrent CRT consisting of 5-FU plus MMC.

PATIENTS AND METHODS

Seven consecutive patients treated with concurrent CRT for ASCC at our institution from October 2007 to February 2010 were enrolled. Data were retrospectively collected from medical charts, including past and present history; laboratory data for the evaluation of HIV infection and hepatic, renal and bone marrow functions; and physiological examination, particularly for the presence of cervical or peri-anal skin cancer. We also collected radiological examinations as follows: computed tomography (CT) of the chest, abdomen and pelvis; magnetic resonance imaging of the pelvis; and colonoscopy with biopsy to confirm the squamous histology. Clinical staging was evaluated according to the American Joint Committee on Cancer (AJCC)—Cancer Staging Manual (18).

All patients of this study received continuous intravenous 5-FU (1000 mg/m^2 on Days 1–4 and 29–32) plus MMC (10 mg/m^2 on Days 1 and 29) and concurrent RT. RT consisted of 59.4 Gy of pelvic RT, with a daily dose of 1.8 Gy. The CT-based RT plan was performed according to the protocol adopted by Radiation Therapy Oncology Group (RTOG) 98-11 (15). Acute toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0). Relative dose intensity was defined as the ratio of the actual dose intensity to the planned dose intensity. Potential RT-related toxicities occurring 90 or more days after the completion of the CRT were classified as late and scored via the RTOG late radiation morbidity scoring schema.

Initial evaluation was performed 2 months after the completion of CRT. Tumour response was evaluated according to the RECIST version 1.0 criteria, with complete response (CR) defined as no residual cancer on either radiological or histological examination. Local recurrence was defined as regrowth after the confirmation of CR. Subsequent follow-up was conducted every 3 months for the first 2 years, then every 6 months thereafter. At each follow-up, patients underwent a physical examination with CT scan. The anal canal was also examined by either colonoscopy or digital rectal examination.

Statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Disease-free and overall survivals from the initiation of concurrent CRT were estimated by the Kaplan–Meier method. Written general consent that included research uses of clinical data had been obtained from all patients, and the study was performed in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiological research. We obtained an institutional review board (IRB) waiver to conduct this study from the chairperson of the IRB.

RESULTS

Baseline Characteristics

The patients consisted of two males and five females, with a median age of 70 years. All patients were negative for HIV infection. Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 in five and two patients, respectively. Baseline clinical stages were II, IIIA and IIIB in four,

Table 1. Acute toxicity of chemotherapy and radiation

	Toxicity grade ($n = 7$)				Grade 3/4
	1	2	3	4	
Haematologic, (*n*)					
Leukopenia	0	1	3	1	4 (57%)
Neutropenia	0	0	4	1	5 (71%)
Haemoglobin	2	3	0	0	0
Thrombocytopenia	1	3	2	0	2 (28%)
Non-haematologic, (*n*)					
Alopesia	3	0	0	0	0
Anorexia	3	2	0	0	0
Colitis	0	0	0	0	0
Constipation	1	0	0	0	0
Diarrhoea	3	2	0	0	0
Dermatitis associated with radiation	0	0	7	0	7 (100%)
Febrile neutropenia	0	0	1	0	1 (14%)
General fatigue	2	0	0	0	0
Mucositis (stomatitis)	2	0	0	0	0
Nausea	3	2	0	0	0
Pain	0	2	5	0	5 (71%)
Vomiting	2	0	0	0	0

one and two patients, respectively. All primary tumours were pathologically diagnosed as squamous cell carcinoma.

Treatment Compliance and Tumour Response

All patients received full-dose RT (59.4 Gy), with a median treatment duration of 49 days (range: 46–55). Irradiation was temporarily interrupted in one patient due to an episode of grade 3 febrile neutropenia that persisted for 4 days, but was restarted immediately after recovery and eventually completed. A second patient had grade 4 neutropenia without fever after the first cycle, after which the dose was reduced for the second cycles to 80% for both 5-FU and MMC without any interruption of RT. The median relative dose intensities of 5-FU and MMC were both 99%. Initial evaluation after the completion of treatment showed a complete response in all patients.

Toxicity

The acute toxicities are listed in Table 1. Acute grade 4 haematologic toxicity included leukopenia in 14% (1/7) of patients and neutropenia in 14% (1/7). Acute grade 3 or greater non-haematologic toxicity included febrile neutropenia in 14% (1/7), dermatitis in 100% (7/7) and pain in 71% (5/7). There were no treatment-related deaths. In terms of late toxicity of RT, one patient developed mild rectal incontinence, which did not require colostomy.

Survival

At a median follow-up of 37.5 months (range: 22–49 months) as of data cut-off in December, 2011, only one patient with initial clinical stage II (T2N0M0) had experienced recurrence and undergone salvage APR with a clear negative margin due to local recurrence 9 months after confirmation of CR. The 3 year disease-free survival rate for all patients was 83.3% (Fig. 1). All patients remain alive and cancer-free.

DISCUSSION

In this study of concurrent CRT for ASCC, we found that all seven patients achieved a complete response at initial evaluation. Although RTOG 98-11 did not report a response rate, all patients in our study achieved CR. Further, the 3 year disease-free and overall survivals at a median follow-up of

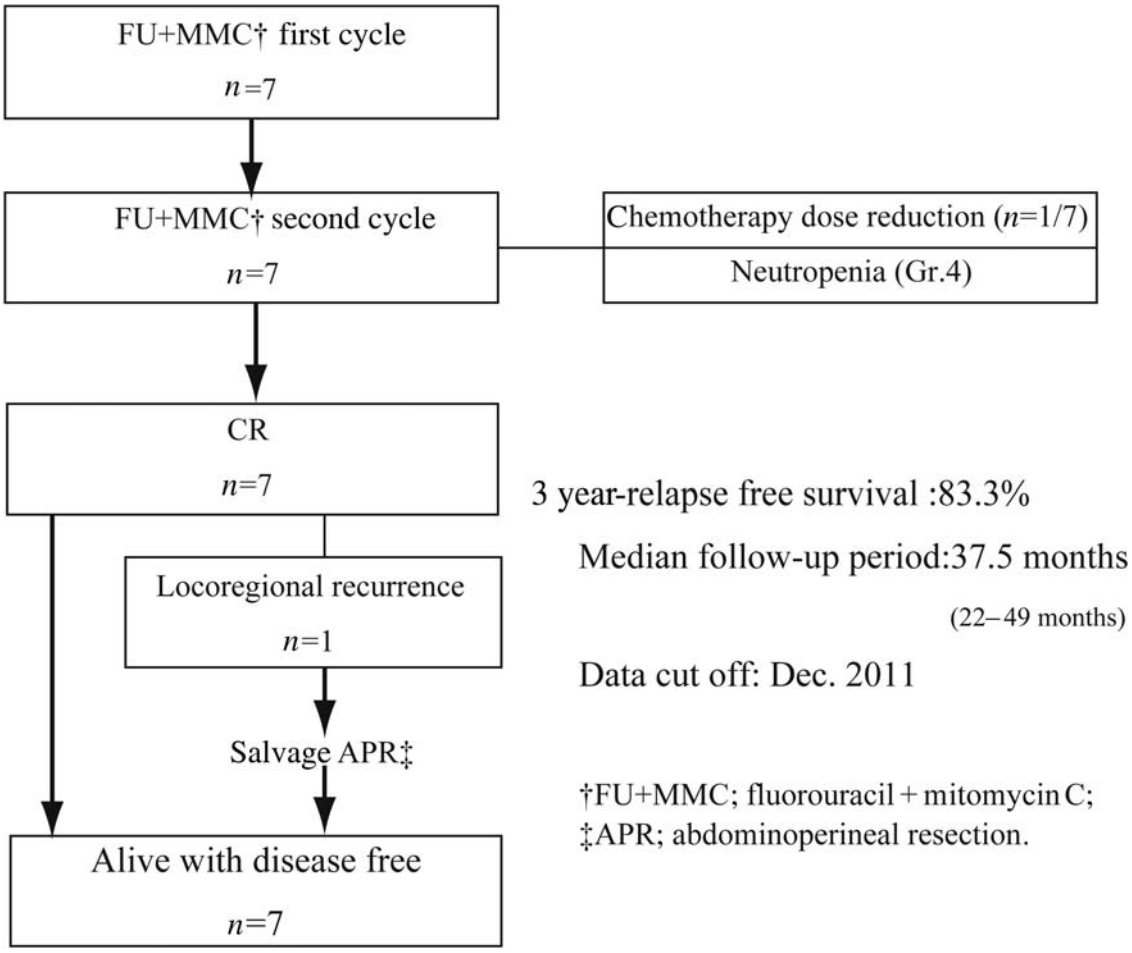

Figure 1. Total profile ($n = 7$).

37.5 months in our study were 83.3 and 100%, when compared with 67 and 84% in RTOG 98-11, respectively.

Twenty-nine percent of the patients in our study were male and had clinically positive nodes (31 and 26% in RTOG 98-11, respectively), and 43% had tumours larger than 5 cm in diameter (27% in RTOG 98-11), which are independent prognosticators for poor overall survival. The poor prognosticators in this study were consistent with those in RTOG 98-11. Allowing for the substantial limitations of our study, principally the small number of patients due to the very low incidence of ASCC and the study design as a single institution retrospective study, these efficacy results are considered comparable to those in the West. To our knowledge, this is the first report to suggest that concurrent CRT using 5-FU plus MMC might be effective in Japanese patients with ASCC.

In terms of treatment compliance, this CRT is considered to be tolerable for Japanese patients with ASCC: the completion rate of RT was 100%, with a median total dose of 59.4 Gy (versus 91% with a median total dose of 55 Gy in RTOG 98-11), and the median relative dose intensities of 5-FU and MMC were 99% for both (versus 95% in RTOG 98-11).

With regard to acute toxicity, the rates of non-haematologic grade 3 or greater toxicities were dermatitis in 100% (versus 48% in RTOG 98-11), febrile neutropenia in 14% (versus 29% in RTOG 98-11) and pain in 71% (versus 44% in RTOG 98-11). The rates of acute haematologic grade 3 or greater toxicities were leukopenia in 57%, neutropenia in 71% and thrombocytopenia in 28% (versus 61% in RTOG 98-11 blood/bone toxicity). These results suggest that concurrent CRT with FU plus MMC is likely tolerable in Japanese patients, as it is in Western populations.

Regarding the late toxicity of RT, one patient developed mild rectal incontinence, which did not require a colostomy. The incidence of late toxicity of RT, such as anal ulcer, stenosis and necrosis, is reported to be dose-dependent. In a review of late radiation-induced toxicities in 144 patients with anal cancer who were treated with either RT alone or with chemotherapy, the 5 year follow-up results showed a rate of APR indicated for late treatment-related complications of 10% (19). These findings suggest the need for careful attention to the late toxicity of RT, although none of our present patients have required either APR or colostomy, with a median follow-up period of 37.5 months to date.

In conclusion, this study suggests that concurrent CRT with FU plus MMC might be tolerable and effective in Japanese patients with ASCC.

Conflict of interest statement

None declared.

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